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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,279	10/21/2002	John Philip Tite	PG37998	5192

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,279	TITE, JOHN PHILIP	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/26/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending in the application, and under current examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Pape et al* (Immunol Rev 1997;156:67-78, IDS/CC), in view of *Searle et al* (Cancer Metastasis Rev 1996;15:329-49, IDS/CB), and *Chen et al* (J Gen Virol 1999;80:1393-9).

Pape et al disclose a method for assaying a T-cell response for the study of T cell activation in vivo, wherein the method comprises transferring into normal mice T-cells from syngenic TCR-transgenic mice (TCR-T cells from DO11.10 TCR-transgeneic mice, column 1, page 69), followed by administering an antigen (ovalbumin) correspondent to the TCR expressed on the surface of the TCR-T cells of DO11.10 TCR-transgenic mice (column 2, page 71). They then assessed an immune response associated with said TCR-T-cells by monitoring the number and anatomical location of the TCR-T cell population (e.g. fig. 5, and table 1)

using antibody kj26, which was raised specifically recognizing the surface marker of the transgenic TCR heterodimers. *Pape et al* also teach obtaining a sample containing TCR-T cells from recipient mice after step b, and re-stimulating said TCR-T cells with the same antigen ovalbumin before assessing for cytokine production, wherein the cytokines assessed include IFN-gamma and IL-5 (e.g. paragraph bridging pages 72 & 73, and table 1). *Pape et al* tested T helper cell response (CD4+) by depletion of CD8+ T cell population before adoptive transfer of TCR-T cells (column 2, page 69). *Pape et al* go on to teach the advantage and necessity of the disclosed assay method. *Pape et al* reviewed difficulty in the art for tracking the T cell population during an immune response, and stated, "WE HAVE DEVELOPED AN INTERMEDIATE STRATEGY THAT RELIES ON THE ADOPTIVE TRANSFER OF TCR-TRANSGENIC T CELLS INTO SYNGENEIC NORMAL RECIPIENTS... THIS MANEUVER PRODUCES A PEPTIDE/MHC-SPECIFIC T CELL POPULATION THAT IS LARGE ENOUGH TO BE EASILY DETECTED BY FLOW CYTOMETRY FOLLOWING STAINING WITH AN ANTI-CLONOTYPIC ANTIBODY, BUT SMALL ENOUGH TO BEHAVE IN A PHYSIOLOGICAL MANNER WHEN CONFRONTED WITH ANTIGEN IN VIVO" (column 1, page 69). *Pape et al* illustrated the use of the method for studying immune response induced by an antigen protein, but not a nucleic acid encoding an antigen, and *Pape et al* do not teach an assay that is indicative of a cytotoxic T-cell (CTL) response.

Searle et al supplemented the teaching of *Pape et al* by establishing that a nucleic acid encoding an antigen is an alternative to an antigen-induced CTL to cancer or infectious pathogens, and both can induce a protective immune response (e.g. abstract and 1st paragraph, page 329). *Searle et al* teach the

advantage to use gene transfer for tumor specific antigen vaccination and gene gun technique in introducing the nucleic acid into the host for inducing a CTL response (e.g. page 337). *Searle et al* teach a nucleic acid encoding an antigen and other therapeutic agents such as cytokines and co-stimulatory factors can potentially lead to a longer-lasting presence of the antigen for immune stimulation and the co-stimulating agents could reverse the lack of T cell response to tumor antigens (e.g. pages 330 and 342). *Searle et al* concluded that improved understanding of the immune system has generated possibilities to enhance the generation of tumor-specific CTLs, and gene transfer techniques are central to many of these", while pointing out further clinical and animal studies are needed. The teaching of *Searle et al* provides motivation to use the method taught by *Pape et al* in the study of nucleic acid-induced immune response. *Searle et al* do not teach particular assays that are indicative of a CTL or a memory response.

Chen et al supplemented the teaches of *Pape et al* in view of *Searle et al* by illustrating the well-known assays in the art indicative of CTL and memory T cell responses (column 2, page 1394, CTL assay; and § Results, memory T cell).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method taught by *Pape et al,* for studying nucleic acid-induced immune response as taught by *Searle et al* with the aid of numerous art-known assay methods as taught by *Pape et al* and *Chen et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because the need for developing DNA vaccine as taught by *Searle et al* and the advantage of the assay method for tracking T cell

populations as taught by *Pape et al.* Given the knowledge and levels of the skilled in the art, the skilled in the art would have had a reasonable expectation of success of using the tracking method as taught by *Pape et al* in studying DNA vaccination as taught by *Searle et al.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adoptive transfer of TCR-T cells from a DO11.10 transgenic mouse to a syngenic recipient for assessing a T cell response to ovalbumin, does not reasonably provide enablement for assessing a T cell response to any nucleic acid encoding an antigen, wherein the TCR-T cells are allogenic/xenogenic, and wherein TCR-T cells are not from a transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These

factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given broadest reasonable interpretation, the claimed invention is drawn to a method for assessing an *in vivo* T cell response to a nucleic acid encoding an antigen administered into a mammal. The specification teaches that the method is to use adoptive transfer technique to monitor T cell responses in vivo through an assessment of the expansion, surface markers of the transferred T cells, and cytokines produced by these T cells. With respect to the starting materials of the method, i.e. the TCR-T cells, the specification teaches that such cells may be produced 1) *in vitro* by transforming splenocytes with a DNA encoding a specific T cell receptor, 2) obtained from a TCR transgenic mammal, or 3) clonal expansion of T cells by re-stimulation of pre-immune splenocytes with APCs presenting antigens specific for the T-cell receptor (Specification, page 4, lines 5-15).

With respect to TCR-T cells produced by the third method, i.e. clonal expansion, *Pape et al* (IDS) teach, "T CELL CLONES ARE RELATIVELY LOCKED INTO ONE TYPE OF RESPONSE PATTERN AND ARE NOT FREE TO DIFFERENTIATE ALONG THE MULTIPLE PATHS THAT ARE AVAILABLE TO NAÏVE T CELLS AS THEY RESPOND TO ANTIGEN IN VIVO" (1st

paragraph, page 68). In view of such teaching, this population of TCR-T cells does not appear to be enabled as the starting material of the claimed invention.

With respect to TCR-T cells produced by the first method, it requires identification, isolation and sequencing of the TCRs, raising antibodies that only recognize a specific TCR heterodimers, and highly sensitive detection method. To this end, *Pape et al* teach, "FOR MOST ANTIGEN-SPECIFIC RESPONSE, THE TCR USAGE OF THE RESPONDING CLONES IS UNKNOWN. THEREFORE, EVEN IF THE SENSITIVITY OF FLOW CYTOMETRY OR IMMUNOHISTOLOGY COULD BE IMPROVED, ANTI-TCR ANTIBODIES THAT BIND EXCLUSIVELY TO A DEFINED ANTIGEN-SPECIFIC T CELL POPULATION ARE NOT AVAILABLE" (2nd paragraph, page 68). Apparently, the difficulties include identification of the TCR, availability of the antibody, and sensitivity of the detection method. Moreover, even if such TCR has been isolated and sequenced, and are readily available for splenocytes transformation, the specification fails to teach the *in vivo* behavior of such transformed T population, whether the *in vitro* transformed T cells could uniformly carry and efficiently expressing the TCR on their surface, and whether the TCR expression construct would pass on to progenies upon antigen stimulation, clonal expansion, and subclonal differentiation. Without sufficient passage of the TCR transgene to clonal expanded and differentiated T cell subpopulations, T cell response in vivo cannot be properly measured. In view of such, it would have required excessive undue experimentation for the skilled in the art intending to practice the invention.

With respect to TCR-T cells produced by the second method, the specification fails to disclose other TCR-transgenic animals known in the art

beyond the DO11.10 disclosed by *Pape et al.* Thus, in addition to identification of the TCR and production of the antibody, this method further requires production of a transgenic animal, which further requires sophisticated technology and extended time period. For each type of antigen-specific TCR, and each type of antigen, a distinct transgenic animal line is needed. In view of such, it does not appear that the claimed method could be used as a routine procedure for assessing T cell response for any nucleic acid vaccine beyond the ovalbumin, and it would have required excessive undue experimentation for the skilled in the art intending to practice the invention.

The claims further read on transferring allogenic and even xenogenic TCR-T cells to a mammal, which is known in the art to necessarily elicit an immune response to the allogenic or xenogenic TCR-T cells, and such response would interfere with the assessment of a nucleic acid vaccine-induced immune response. In view of such, the claimed invention does not appear to be enabled for its full scope.

Therefore, in view of the limited guidance, the knowledge of the skilled in the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is

571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram R. Shukla** can be reached on 571-272-0735. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QJL
March 7, 2005